PATENT
Customer No. 22,852
Attorney Docket No. 06478-1454.00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Thomas WEIMAR	Group Art Unit: 1631
Application No.: 09/833,675	Examiner: Cheyne D. Ly
Filed: April 13, 2001	
For: PROCESS FOR FINDING OLIGONUCLEOTIDE SEQUENCES FOR NUCLEIC ACID AMPLIFICATION METHODS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY TO OFFICE ACTION

Applicant now responds to the Office Action mailed October 8, 2003. A three month Petition for Extension of Time and the requisite fee are also enclosed. For the reasons discussed below, Applicant traverses all of the rejections and respectfully requests consideration.

REMARKS

Status of the Claims

Claims 10-34 are pending in the present application. Claims 26-34 are withdrawn from consideration. Claims 10-25 are rejected under 35 U.S.C. §§ 103 and 112 in the outstanding Office Action. Applicants note that the rejection of claims 10-25 under 35 U.S.C. § 102(a) from the previous Office Action is not reiterated, and hence, is

withdrawn. (*See* Office Action, paragraph 1). No amendments to the claims have been made.

Rejection of Claims 10-25 under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 10-25 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter of the invention (*See* Office Action, paragraph 3). The Examiner maintained this rejection, as recited in the previous Office Action mailed May 27, 2003, and provided additional remarks. In particular, the Examiner asserts that the phrase "mutually overlaps" in claims 10-25 is indefinite (*See* Office Action, paragraph 6). Furthermore, the Examiner states that the term "universal" in claims 20 and 21 is indefinite (*See* Office Action, paragraph 8). Finally, the Examiner contends that the term "completely" in claim 22 is indefinite (*See* Office Action, paragraph 10). Applicant respectfully traverses these rejections and provides the following remarks.

"Mutually Overlapping"

The Examiner states that the phrase "mutually overlapping" causes the claim to be vague and indefinite because it is unclear what criteria are being used to determine that a nucleic acid "mutually overlaps" with another. Specifically, the Examiner maintains that it is unclear whether the "mutually overlapping" oligonucleotide sequences are "identical polynucleotide sequences or complementary of sense with anti-sense sequences." (Office Action, paragraph 6). The Examiner also questions whether the "overlapping DNA molecules are single or double stranded." (Office Action, paragraph 6).

Applicant asserts that the phrase "mutually overlapping" is not vague or indefinite, since it is well-known to those of skill in the art. In claims 10, 13-16, and 20, the phrase "mutually overlapping" is used to describe "oligonucleotide sequence fragments." To one with ordinary skill in the art, an oligonucleotide is a single-stranded nucleotide sequence. As defined in the The Encyclopedia of Molecular Biology, an oligonucleotide is "[a] short length of single-stranded polynucleotide chain usually <30 residues long." (The Encyclopedia of Molecular Biology, page 767 (Sir John Kendrew & Eleanor Lawrence eds., Blackwell Science 1994)). Similarly, Current Protocols in Molecular Biology includes "two single-stranded oligonucleotide primers" in a list of the components required for PCR—one of the methods for amplifying a target nucleic acid described in this invention (Current Protocols in Molecular Biology, page 15.0.3 (John Wiley & Sons 1998)). Finally, the textbook Principles of Biochemistry's definition of oligonucleotide of "a short nucleic acid" is accompanied by a schematic drawing of a single-stranded nucleic acid. (Principles of Biochemistry, page 329 (Albert L. Lehninger, David L. Nelson & Michael M. Cox eds., Worth Publishers 1993)). Therefore, to one skilled in the art, the phrase "mutually overlapping oligonucleotide sequence fragments" clearly refers to single-stranded fragments and not double-stranded fragments.

In addition, the phrase "mutually overlapping" is not vague when read in the context of the rest of the claim and the specification (page 3, line 16 to page 4, line 9). For example, page 3, lines 20-24 of the specification refer to "mutually overlapping sequence fragments, which preferably comprise from 30-50 bases . . . ." Since the specification refers to these "sequence fragments" as "bases," as opposed to "base

pairs," one skilled in the art would necessarily recognize that the "mutually overlapping oligonucleotide sequence fragments" are single-stranded.

This section of the specification generally relates to a process for finding oligonucleotide sequences for nucleic acid amplification. To one with ordinary skill in the art, the process of nucleic acid amplification requires single-stranded oligonucleotides. In a typical PCR reaction—one common type of nucleic acid amplification—the DNA to be amplified is first denatured by heating the sample. Then, in the presence of DNA polymerase and dNTPs, single-stranded oligonucleotides hybridize specifically to the target sequence to prime new DNA synthesis. After DNA synthesis, this cycle is repeated to generate multiple copies of the target DNA. (*See* J. Sambrook et al., Molecular Cloning: A Laboratory Manual, page 15.0.3, figure 15.0.1 (Cold Spring Harbor Laboratory Press 1989)). For PCR to work, the oligonucleotides must be single-stranded so they can hybridize to the target sequence. Thus, "mutually overlapping oligonucleotide sequence fragments" must refer to single stranded oligonucleotides.

One with ordinary skill in the art would also recognize that the phrase "mutually overlapping oligonucleotide sequence fragments" refers to fragments that have identical sequences in the "overlapped" sequence. The claims and specification describe a process for identifying heterologous oligonucleotide sequences for amplifying a target nucleic acid sequence that includes fragmenting one or more conserved regions of the target nucleic acid sequence to be amplified to generate "mutually overlapping oligonucleotide sequence fragments." Thus, when the sense and anti-sense strands of the target sequence to be amplified are fragmented, each fragment will be composed of

some portion of the conserved region. When these single stranded oligonucleotide fragments are lined up, the fragments will "overlap" at their ends where they share an identical portion of the target sequence. Therefore, when read in the context of the claims and specification, the "mutually overlapping" regions of the oligonucleotide sequence fragments are regions with identical sequences, rather that sequences that are complementary to each other.

"Universal"

The Examiner states that the term "universal" of claims 20 and 21 is indefinite because "it is unclear what criteria are being used to determine that a specific base is 'universal' (a base can be found any where in the universe or applicable to all purposes)." (Office Action, paragraph 8). As pointed out in Applicant's July 29, 2003 Response, claim 21 is a dependent on claim 20 and specifically limits the universal base to inosine. Therefore, Applicant assumes that the Examiner's indefiniteness rejection with respect to the term "universal" applies only to claim 20.

Applicant asserts that the term "universal" is not vague or indefinite, since it is well-known to those of skill in the art. In claims 20 and 21, and in the specification (page 5, lines 4-10), the term "universal" is used in the phrase "universal base." To one with ordinary skill in the art, a "universal base" is a nucleotide base that can hybridize non-selectively to each of the native bases: A, T, G, and C. (M. Berger et al., Universal Bases for Hybridization, Replication, and Chain Termination, Nucleic Acids Research, 28(15):2911-2914 (2000); F. Hill et al., Polymerase Recognition of Synthetic Oligodeoxyribonucleotides Incorporating Degenerate Pyrimidine and Purine Bases, Proc. Natl. Acad. Sci., 95:4258-4263 (1998)). Berger et al. defines "universal bases" as

"hydrophobic base analogs without hydrogen bonding groups that pack efficiently in duplex DNA . . . [that] show little selectivity in pairing with native bases" (page 2911, first paragraph of Introduction). Berger et al. also notes that "[s]uch 'universal' bases have attracted much attention due to their potential ability in the design of oligonucleotide primers or hybridization probes where the identity of one or more bases in the target sequence is unknown" (page 2911, first paragraph of Introduction). Similarly, Hill et al. notes that "[a] universal base that is capable of substituting for any of the four natural bases in DNA would be of great utility in both mutagenesis and recombinant DNA experiments" (page 4258, Abstract). Therefore, it is well-established that the term "universal base" as used in the prior art, refers to a base that can hybridize with all native bases.

"Universal base" is also not indefinite when read in light of claim 21 and page 5, lines 4-10, of the specification. Claim 21 limits the "universal base" to inosine. It is well-known in the art that inosine "forms stable base pairs with all four conventional bases" (Molecular Cloning: A Laboratory Manual, page 11.17 (J. Sambrook, E.F. Fritsch, & T. Maniatis eds., 2d ed. 1989)). Hill et al. also notes that "[m]any publications attest to the successful use of deoxyinosine" as a "universal base" and that "it base pairs with the four normal bases" (page 4258, first paragraph). Thus, the juxtaposition of the words "universal base" and "inosine" in claim 21 and on page 5, further supports the idea that the term "universal base" refers to a base that can hybridize with all the native bases.

The publications referenced above were submitted with the Information Disclosure Statement filed in this application on April 6, 2004.

"Completely"

The Examiner states that the term "completely" of claim 22 is indefinite because it is unclear what criteria are being used to determine that a nucleic acid is "completely" hybridized (*See* Office Action, paragraph 10).

Applicant asserts that the term "completely" is not vague or indefinite, since its meaning is well-known to those of skill in the art when viewed in light of the claims and specification. As described above, a universal base, such as inosine, can hybridize with any native base. The specification, on page 5, lines 4-10, describes a process of replacing all mismatched bases with a universal base, "thereby making it possible to achieve complete hybridization." As such, the purpose of replacing mismatched bases with a universal base is to achieve complete, or 100%, hybridization. Thus, when viewed in the context of claims and specification, the term "completely" is not indefinite to one of skill in the art.

Accordingly, Applicant requests that the Examiner withdraw the rejection of claims 10-25 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 10-25 under 35 U.S.C. § 103

The Examiner rejects claims 10-25 under 35 U.S.C. § 103(a) as obvious in view of Neri et al. (U.S. 6,194,149; "Neri") in combination with Chee et al. (U.S. 5,837,832; "Chee") and Tureci et al. (U.S. 6,214,983; "Tureci"). Applicant traverses this rejection and provides the following remarks.

A *prima facie* case of obviousness must meet several essential criteria, including that the prior art references must teach or suggest all of the claim limitations, M.P.E.P.

§ 2142, and that there is some reason, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to combine the teachings of the references in the manner proposed by the Office. *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996); M.P.E.P. § 2143. The combination of references must also provide a reasonable expectation of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The suggestion or motivation must be found in the prior art, not in the Applicant's disclosure. *Id.* Furthermore, the suggestion to combine the prior art teachings must be clear and particular. *In re Dembiczak,* 175 F.3d 994, 999 (Fed. Cir. 1999). Thus, while a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the prior art, that modification is not obvious unless the prior art suggested the desirability of such a modification. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). Judged by this standard, the Examiner has not met his burden for establishing a *prima facie* case of obviousness.

The Examiner has failed to show that all elements of the present invention are present in the cited references. All the claims presently pending in this application depend from claim 10, either directly or indirectly, and therefore incorporate all the limitations of that claim. Neri, however, does not disclose any of the three steps in claim 10 of the present invention: (step a) selecting a target nucleic acid to be amplified; (step b) fragmenting one or more conserved regions of this target to produce mutually overlapping fragments; and (step c) identifying heterologous sequences that are similar to these fragments.

Rather, Neri describes a method of "structure probing," whereby nucleic acid polymorphisms are detected by analyzing the interactions between a folded target

nucleic acid and a nucleic acid probe. Using this technique, a probe can only hybridize with a single-stranded nucleic acid. As a result, a folded target nucleic acid is not available to hybridize with a probe. By measuring rates hybridization rates of specific probes with folded nucleic acid structure, a hybridization signature is identified that, in comparison with other signatures, can be used to detect polymorphisms in the folded target nucleic acid sequence. This is not the purpose of the claimed invention.

As the Examiner admits, Neri does not disclose the limitations described in step b, where one or more conserved regions of a target nucleic acid is fragmented to produce mutually overlapping fragments. (*See* Office Action, paragraph 14).

In addition, Neri does not disclose the identification of heterologous sequences that are similar to these fragments. Instead, Neri discloses the synthesis of probes designed to compare hybridization between different folded target nucleic acids for use in structure probing experiments. These probes are not designed based on their similarity to mutually overlapping fragments of a different species of a target nucleic acid sequence, but rather are designed to detect secondary structure caused by nucleic acid polymorphisms. Therefore, Neri does not disclose all the limitations of step c either.

Contrary to the Examiner's assertion, Chee does not disclose all the limitations described in step b, where one or more conserved regions of a target nucleic acid is fragmented to produce mutually overlapping fragments. The Examiner states that Chee "discloses a method for identifying heterologous oligonucleotide sequences wherein target fragmentation is performed followed by target DNA amplified by PCR with primers." (Office Action, paragraph 15). The Examiner mischaracterizes Chee. Instead, Chee discloses fragmentation of a nucleic acid target for the purpose of

diminishing the percentage of inaccuracies or "miscalled bases" when sequencing a DNA sequence on a gene chip (column 23, lines 12-61)—not for identifying heterologous nucleotide sequences. Chee describes a method for sequencing exon 5 of the p53 gene using a gene chip and comparing it to the known sequence to illustrate the accuracy of sequencing using a gene chip. The p53 sequence generated using the gene chip was 93.5% accurate as compared to the known sequence. Thus, 6.5% of the sequence was incorrectly sequenced, or "miscalled." Chee speculates that these inaccuracies may be due to secondary structure in the target sequence (exon 5 of p53 in this example) and suggests using shorter targets than the 17-mer used in this example to increase the sequencing method's accuracy. This method does not involve fragmenting a target nucleic acid to generate mutually overlapping oligonucleotide sequence fragments to identify heterologous oligonucleotide sequences as in the present invention, but rather discloses a method for increasing the accuracy of sequencing on a gene chip by fragmenting the target sequence to reduce its secondary structure. Unlike the present invention, the reference does not explicitly require that the fragmentation is of a conserved region of the target nucleic acid. Accordingly, nowhere does Chee disclose all the elements of step b of claim 10, as claimed by the Examiner. Likewise, Chee does not disclose the process of identifying one or more heterologous oligonucleotide sequences that are similar to one or more of the mutually overlapping oligonucleotide sequence fragments, as required by step c.

Similarly, Tureci does not disclose any of the limitations in claim 10. The Examiner states that Tureci discloses a method comprising an electronic search of the Gen Bank database to identify known nucleic acid molecules that can be used to

generate primers, as in claim 19. (*See* Office Action paragraph 17). Applicant reasserts that significant differences exist between the database searching in Tureci and the searching described in claim 19, which is dependent on claim 10. The search described in Tureci involves searching GenBank to find all sequences that belong to the synaptonemal complex, by looking for sequences specifically expressed in the testis and associated with meiosis. The identified sequences were then used in a subsequent search of an expressed sequence tag (EST) database. The identified ESTs were then used to design primers for use in RACE analysis, which is used to determine the sequence of the cDNA ends of the ESTs.

The present invention, as described in claim 19, involves using mutually overlapping fragments as query fragments, rather than the functional criteria used in Tureci, to search a DNA database to find heterologous sequences. Thus, the methods for identification of query fragments, and the purposes of the searches in the present invention are very different from those described in Tureci.

Even if the combination of Neri, Chee, and Tureci had disclosed all elements of the present invention, the Examiner has not shown that there is some reason, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to combine the teachings of the references in the manner proposed by the Office. Similarly, the Examiner has not pointed to evidence suggesting a reasonable expectation of success in the prior art, rather than in the Applicant's disclosure. Finally, the Examiner has not identified a suggestion to combine the prior art teachings that is clear and particular.

The only support the Examiner mentions for a motivation to combine is that Neri, Chee, and Tureci are all in fields relating to nucleic acids. (*See* Office Action, paragraph 18). The Examiner states that: (1) Neri discloses improvements for tools to analyze nucleic acid structures directed to clinical research and diagnostics; (2) Chee discloses a diagnostic method for analyzing nucleic acid for diagnostic uses; and that (3) Tureci discloses a method for analyzing nucleic acid molecules. The Examiner then goes on to state that "the improvements disclosed by Neri et al. is directly applicable to the method for analyzing nucleotide molecules for diagnostic uses as taught by Chee et al and Tureci et al." (Office Action, paragraph 18.). The fact that these three references all deal with nucleic acids does not satisfy the Examiner's burden of pointing to a clear and particular suggestion to combine the prior art teachings and do not identify any reasonable expectation of success.

Accordingly, a proper obviousness rejection has not been made and Applicant respectfully requests that the reject of claims 10-25 be withdrawn.

Response to Paragraphs 20 and 21

Although the Examiner has withdrawn the rejection of claims 10-25 under 35 U.S.C. § 102(a) in the present Office Action, he restates in paragraph 20 of the present Office Action that Neri's "Figure 18(a) is identical to the oligonucleotide sequence of SEQ ID NO 1 of this instant application." For the record, Applicant still fails to see the identity of Figure 18(a) in Neri and SEQ ID NO 1.

In response to paragraph 21 of the present Office Action, Applicant notes that claim 18 depends from claim 10, and as such incorporates all of its limitations. As described above, Neri does not disclose the limitations in claim 10.

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: April 7, 2004

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